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10TH ANNUAL
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neuroscience CME

Master Class for Neuroscience Professional Development

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Diabetic Neuropathy: A Global and Growing Problem

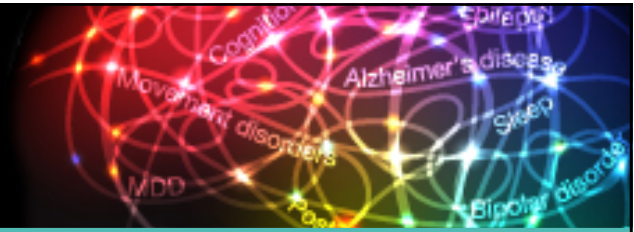
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Disclosures



- ***Research/Grants:*** World Federation of Neurology
- ***Speakers Bureau:*** Grifols USA, LLC
- ***Consultant:*** Baxalta

Learning Objective 1

Review the etiology and epidemiology of diabetic neuropathy.



Learning Objective 2

Differentiate between the different types of diabetic neuropathy.



Learning Objective 3

Select appropriate treatments for patients with diabetic neuropathy.

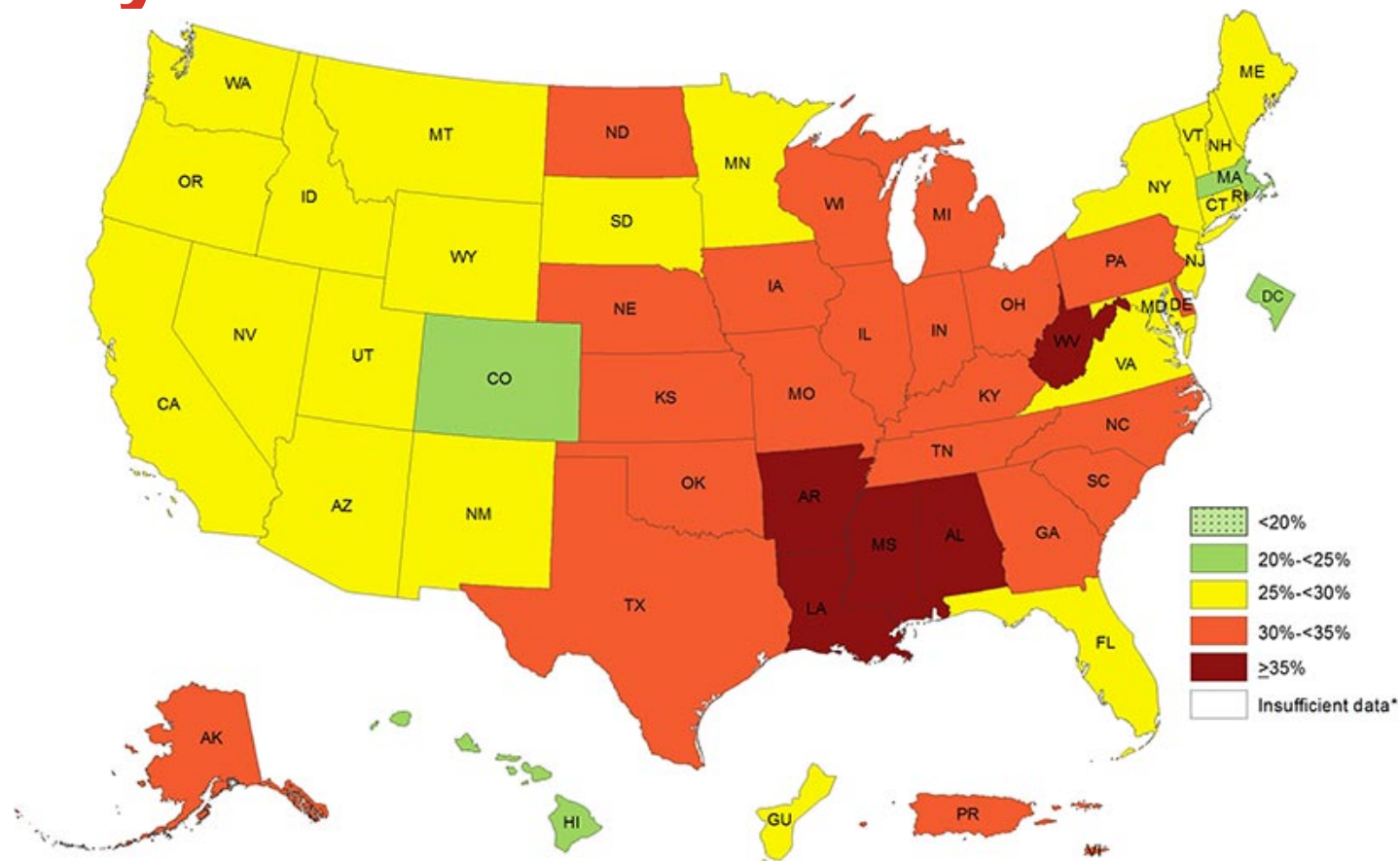


Global Obesity and Overweight 2016



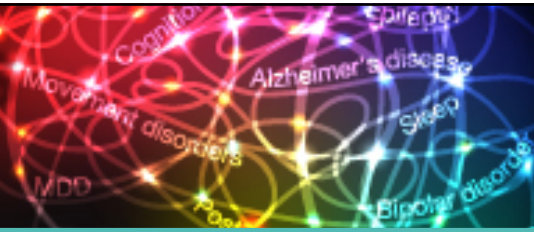
- Obesity has tripled since 1975
- > 1.9 billion adults are overweight
- > 650 million adults are obese
- 39% adults are overweight
- 41 million children < 5 years and 340 million aged 5-19 years are overweight

Obesity Prevalence USA 2016

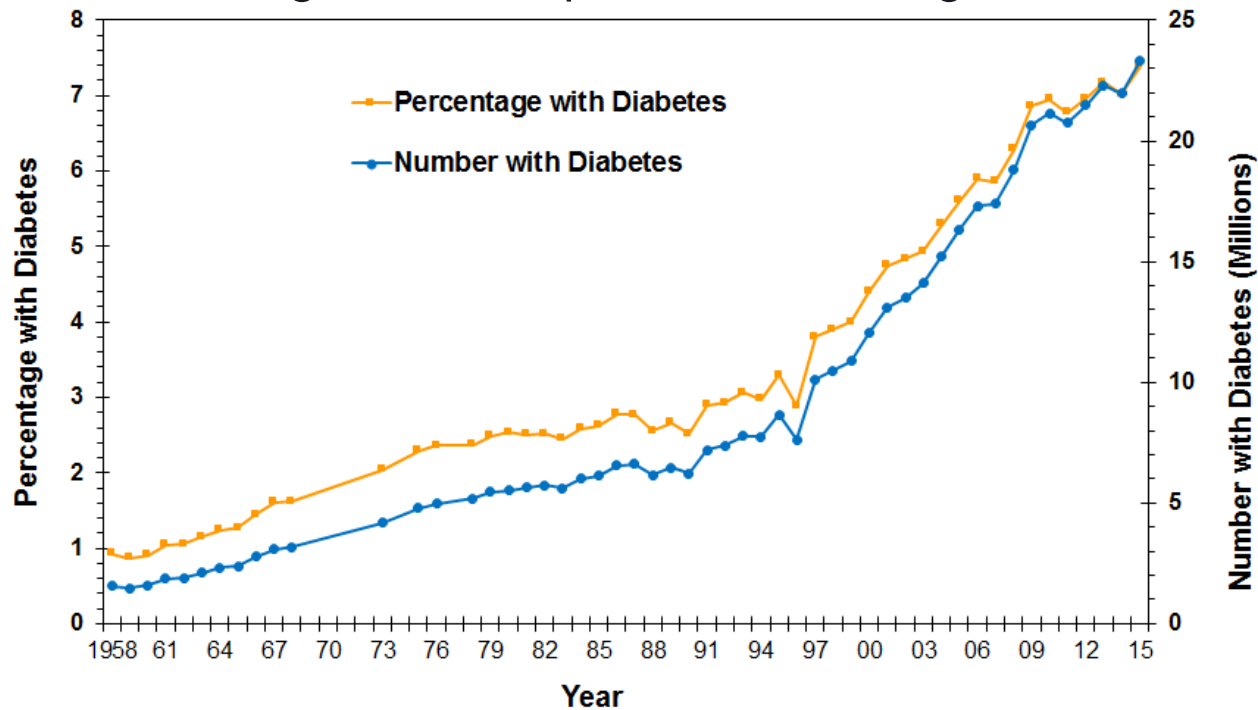


Centers for Disease Control. <https://www.cdc.gov/obesity/data/prevalence-maps.html>

Increasing Rates of Diabetes in the United States



Number and Percentage of US Population with Diagnosed Diabetes, 1958-2015



Centers for Disease Control's Division of Diabetes Translation. US Diabetes Surveillance System.
https://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf.

Diabetic Neuropathy: Epidemiology



- The prevalence of diabetic neuropathy increases with age, duration of diabetes, poor diabetic control
 - In 2014, diabetes affected 422 million people
 - Surge in diabetes prevalence due to increased rates of obesity in developing countries
 - Increased intake of energy-dense foods that are high in fat and increase in sedentary lifestyle
- An estimated 40-50 million people have diabetic neuropathy worldwide
- Good control of diabetes is the best prevention but difficult to achieve

World Health Organization. <http://www.who.int/mediacentre/factsheets/fs311/en/>

Causes of Diabetic Neuropathy



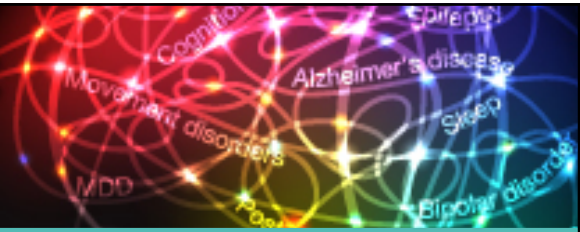
- Poor glucose control
- Lipids
- Metabolic syndrome

Diabetic Neuropathy: Classification



- Length dependent polyneuropathy
 - Early involvement of small fibers
 - Often associated with autonomic neuropathy
- Focal and multifocal neuropathy
- Non-diabetic neuropathies more common in diabetic patients

Length Dependent Diabetic Polyneuropathy

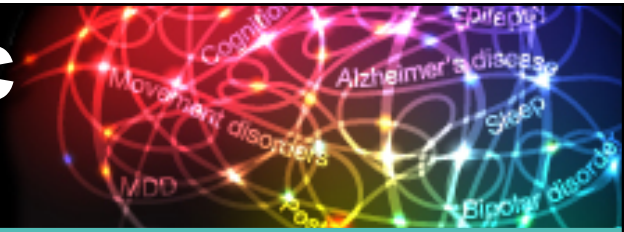


- Small-fiber type¹
 - Impairment of temperature and pain sensations following a length-dependent pattern
 - Relative sparing of position sense, light touch and vibratory sensations
 - Marked autonomic disturbances
 - Normal strength
 - Pseudo-syringomyelic diabetic neuropathy²

1. Misra UK, et al. *Ann Indian Acad Neurol.* 2008;11(2):89-97.

2. Vergely P. *Gaz Hebd Med Chir.* 1893;32:376-381.

Length Dependent Diabetic Polyneuropathy



- Large-fiber type¹
 - Uncommon
 - Light touch, position sense and vibratory sensation predominantly affected, ataxia ("pseudo-tabetic", Charcot, 1890)²
- Mixed pattern
- Distal motor deficit occurs in the most severe forms only

1. Misra UK, et al. *Ann Indian Acad Neurol*. 2008;11(2):89-97.
2. Charcot M. *Arch Neurol (Paris)*.1890;19:318.

Diagnosis of Length Dependent Polyneuropathy in Patients with Diabetes

- Small fiber sensory neuropathy: typical of diabetes
 - EMG optional
- Large fiber polyneuropathy ± motor deficit
 - Consider other causes: CIDP, paraneoplastic neuropathy, dysglobulinic neuropathy; alcoholism
 - EMG, CSF, protein immunoelectrophoresis, antibodies
- Pure motor deficit
 - Motor neuron disease/muscle disease?

EMG = electromyography, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, CSF = cerebrospinal fluid.
Misra UK, et al. *Ann Indian Acad Neurol.* 2008;11(2):89-97.

Complications of Length Dependent Diabetic Polyneuropathy



- Painful diabetic neuropathy
 - Approximately 13-26% of diabetic patients complain of neuropathic pain¹
 - Hyperalgesic diabetic polyneuropathy^{2,3}
 - Diabetic neuropathic cachexia⁴ and acute painful diabetic neuropathy:⁵ loss of weight, burning pains, impotence, depression.
 - No specific morphological findings in painful diabetic polyneuropathy.

1. Ziegler D. *Diabetes Care*. 2009;32(Suppl 2): S414-S419; 2. Pavy FW. *Med News (Philadelphia)*. 1887;24:357-361; 3. Charcot M. *Arch Neurol (Paris)*. 1890;19:318; 4. Ellenberg M. *Diabetes*. 1974;23:418; 5. Archer AG, et al. *J Neurol Neurosurg Psychiatry*. 1983;46:491-499.

Treatment of Painful Polyneuropathy



- Anti-epileptic drugs:
 - Gabapentin 300 to 3600 mg/day*; pregabalin 150-600 mg/day, pregabalin extended release 330 mg/day
- Antidepressants:
 - Amitriptyline*/imipramine*: 25-150 mg/day
 - Duloxetine: 60 mg/day
- Efficacy of amitriptyline; pregabalin & duloxetine: 50%

*Not FDA approved for diabetic peripheral neuropathy.
<https://www.accessfda.gov>

Complications of Length Dependent Diabetic Polyneuropathy



- Trophic changes
 - Foot ulcers
 - Idiopathic bullae (Bullosis diabeticorum)
 - Neuropathic osteo-arthropathy (Charcot joints)
 - Not specific to diabetic neuropathy.
 - Occur in areas with decreased pain sensation and preserved strength
 - Role of diabetic macro- and microangiopathy

Complications of Length Dependent Diabetic Polyneuropathy (cont'd)

- Neuropathic osteo-arthropathy (Charcot joints)
 - Tarsal & tarsometatarsal joints, occasionally ankle joints
 - Painless foot deformity, sometimes of acute onset
 - Painless fractures of metatarsal bones; disruption of articular surfaces, disorganization of joints
 - Penetration of bacteria through neuropathic ulcers can lead to chronic osteomyelitis

Autonomic Diabetic Neuropathy



- Prevalence of cardiocirculatory dysautonomia
- Cumulative data from 22 diabetes centers:¹
 - 25% of patients with type 1 diabetes
 - 34% of patients with type 2 diabetes
 - Loss of R-R variations (Valsalva test, breathing)
 - Resting tachycardia
 - Fixed heart rate
 - Postural hypotension
 - Asymptomatic; dizziness upon standing, postural syncope.
 - Management of postural hypotension:
 - High salt intake; elastic stockings
 - Pharmacological:
 - Midodrine: 10-30 mg/day²
 - 9 α fluorohydrocortisone: 0.1-0.2 mg/day to 0.4 -0.6 mg/day³

1. John D. England, MD. Autonomic Diabetic Neuropathy Survey. Data on File.;

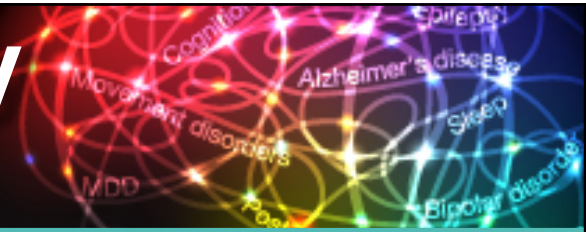
2. FDA. <https://www.drugs.com/pro/midodrine.html>; 3. Figueroa JJ, et al. *Cleve Clin J Med* 2010;77(5):298-306.

Focal and Multifocal Diabetic Neuropathy



- Cranial neuropathy
- Thoracic neuropathy
- Proximal diabetic neuropathy
- Multifocal diabetic neuropathy

Cranial Diabetic Neuropathy Oculomotor Palsies



- Third nerve palsy is the most common
 - Affects mainly patients with type 2 diabetes > 50 yrs.
 - Onset with frontal pains, within 1 or 2 days
 - The third nerve palsy is often complete; pupillary sparing. Spontaneous & complete recovery within 2-3 months.
 - Nerve ischemia on post-mortem study¹
- The sixth nerve is also frequently involved, the fourth seems seldom affected
- Management: MRI to exclude another cause – no treatment needed

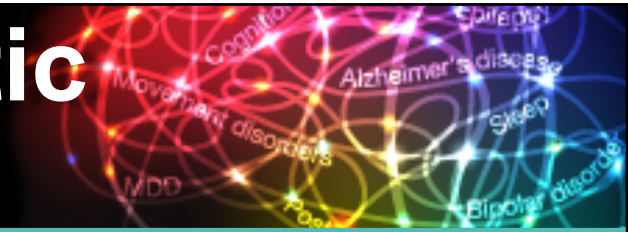
1. American Academy of Ophthalmology. <https://www.aao.org/bcscsnippetdetail.aspx?id=f33e290f-49d9-4643-9bee-705907fc164>; 2. Asbury AK, et al. *Brain*. 1970,93:555-566.

Proximal Diabetic Neuropathy



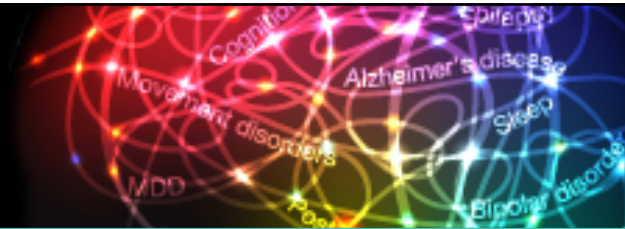
- Rapid onset of pains of the anterior aspect of the thigh of the burning type, worse at night and increased with contact in a patient over 40 years of age
- Progression of neurological manifestations over several weeks in most cases
- Early quadriceps amyotrophy, weakness of psoas & quadriceps muscles, sometimes mild distal weakness too
- Simultaneous bilateral involvement is rare
- Early loss of ipsilateral patellar reflex
- Association with asymptomatic distal symmetrical polyneuropathy

Thoraco-Abdominal Diabetic Neuropathy



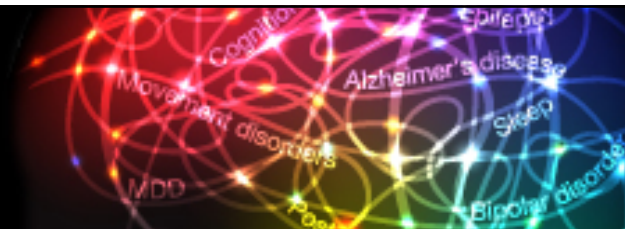
- Thoraco-abdominal neuropathy occurs in type 2 diabetics.
- It is unilateral or predominantly so.
- The onset is abrupt or rapid, with pains or dysesthesias. The pain has a radicular distribution and is made worse by contact and at night.
- Weakness of abdominal muscles occurs.

Conclusions



- Obesity is a global problem
- Most of the world's population live in countries where overweight and obesity kill more people than underweight
- Diabetes is a global problem
- The complications of obesity and diabetes are increasing in prevalence
- These are **preventable!**

Call to Action



- Encourage patients with diabetes to manage their disease stringently in order to prevent diabetic peripheral neuropathy as well as other complications
- Initiate treatment with medications for management of diabetic peripheral neuropathy when appropriate

Questions & Answers



Don't forget to fill out your evaluations to collect your credit.

